REMARKS

Claims 1, 3-11, 13-45, 62-65, 95-101, 106-113, 117, and 123 are pending in the application. Applicants have canceled claims 6, 10, 34-45, 62-64, 95-101, and 106-112 without prejudice or disclaimer, particularly without prejudice to any possibility of rejoinder. Applicants have amended claims 1 and 22. Claims 31, 32, 65, 113, and 117 remain withdrawn. Accordingly, claims 1, 3-5, 7-9, 11, 13-33, 65, 113, 117, and 123 will be pending in the application upon entry of the claim amendments presented herein. *No new matter has been added.*

Applicants have amended claim 1 and 22 to more particularly point out that which Applicants regard as the invention. Support for the amendments can be found throughout the specification and in the claims as originally filed. In particular, support for the amendment to claim 1 may be found at least in claims 1 and 6 as originally filed. Support for the amendment to claim 22 may be found at least in claim 22 as originally filed.

Amendment and cancellation of the claims herein is not are not be construed as acquiescence to any of the rejections/objections set forth in the instant Office Action and were done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the claims as originally filed or similar claims in this or one or more subsequent patent applications.

Applicants appreciate the Examiners withdrawal of the rejections of claims 17, 20 and 21 under 35 U.S.C. §112, second paragraph. However, Applicants request reconsideration of the subject application with respect to the remaining rejections based on the following remarks.

INITIAL REMARKS

Prior to further response, Applicants wish to clarify a misconception/misunderstanding apparent in the remarks of the outstanding Office Action related to the language "chemical alteration." The Office Action has suggested that "solubilization is encompassed by chemical alteration," and specifically points to a *subset* of the text that is included in the definition

provided in the instant specification for this term. Applicants respectfully disagree and provide the following arguments and evidence in support thereof.

Firstly, and significantly, the language cited by the Examiner within the text of the definition of "chemical alteration" has been taken out of context. For sake of convenience, Applicants have provided the relevant excerpt from the specification related to the definition of the language "chemical alteration"

> The language "chemical alteration" is intended to include any chemical reaction of a molecule that is not a chemical digestion. In certain embodiments, the chemical alteration of a molecule produces a chemically or physically, *e.g.*, solubilization, altered molecule. In certain other embodiments, the chemical alteration does not produce a chemically or physically altered molecule, i.e., catalysis has occurred

Applicants emphasize, above all, that the chemical alteration, while possibly producing *altered* molecules that are soluble, ***must involve a chemical reaction at the very least***. Moreover, it was the intention of this definition, and a definition consistent with the understanding of the ordinarily skilled artisan, to provide language that would contrast two types of chemical reactions. One type of chemical reaction involves a strict breaking down reaction of a molecule into fragments, while the other type of chemical reaction simply involves a "chemical transformation or change," as described in the definition of the language "chemical reaction" on page 8, lines 1- 2 of the instant specification. It would be clear to the ordinarily skilled artisan that the term ***chemical*** alteration was not intended to encompass purely *physical* changes alone such as "solubilization." In fact, the ordinarily skilled artisan would understand, that a physical change, such as solubilization, may occur as a result of a chemical reaction or chemical alteration, but that solubilization on its own, is a ***physical*** change (and not a chemical change). As such, the interpretation set forth in the Office Action is not consistent with the knowledge of the ordinarily skilled artisan, and is therefore improper.

Claim Rejections – 35 U.S.C. §112

Claims 9, 11-30, and 33 are rejected under 35 U.S.C. §112, first paragraph

Claims 1-9, 11-30, and 33 are rejected, in that the specification allegedly does not reasonably enable any person skilled in the art to make and use the invention commensurate in scope with the claims. In particular, the prior office action alleged that the specification does not enable a method of enhancing any chemical reaction of any molecule. Applicants respectfully disagree and traverse the rejection.

However, without acquiescing in any way to the rejection and solely in order to expedite prosecution of the application, Applicants have amended claim 1 to incorporate the limitations of claim 6, which now additionally recites "wherein the biomolecule is selected from the group consisting of a protein and a peptide."

Applicants reiterate that the scope of the disclosure related to biomolecules provided should be sufficient to enable the scope of originally file claim 1. However, at the very minimum, Applicants assert that the scope of the disclosure related to proteins and peptides provided should be sufficient to enable the scope of the presently amended claim 1. In this regard, Applicants respectfully direct the Examiner's attention to MPEP § 2163, which states:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus ... See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus....

> ***What constitutes a "representative number" is an inverse function of the skill and knowledge in the art.*** Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed...
>
> Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. For example, in the molecular biology arts, if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acids encoding a given amino acid sequence, but not necessarily any particular species. Cf. *In re Bell*, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) and *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). (Emphasis Added)

Based on the explicit language of the Office Action on page 4, the Examiner has admitted that the level of skill is relatively high, and the knowledge in the art is significant enough to make comment. Accordingly, as noted in the passage above, the number of species sufficient to constitute a "representative number" that would support a given genus is inversely related to these factors. In this respect, Applicants assert that the full scope of the claims relating to the chemical digestion and/or chemical alteration of a protein or peptide is enabled under 35 U.S.C. §112.

In particular, Applicants' specification enables the scope of the amended claims by disclosing numerous examples of chemical digestion and alteration of biomolecules, *e.g.*, proteins and peptides. Example 3, Table 2, and Figure 2 clearly show an increase in digestion of various biomolecules in the presence of a surfactant of formula I. Examples 4 and 5 also demonstrate the digestion of various biomolecules in the presence of a surfactant of formula I. Additionally, Example 8 and Figure 5 shows a chemical alteration of a disulfide bond in the presence of a surfactant. Specifically, Figure 5 demonstrates the reduction of a disulfide bond both in the presence and absence of a surfactant. Applicants therefore contend that the numerous working examples provided in the specification fully enables the scope of the amended claims.

The Office Action admits, for example on page 9 (last full paragraph) that the application is enabled for BSA, lysozyme, ovalbumin, ubiquitin, and bacteriorhodopsin. In this respect, and for further clarification, Applicants, citing Wikipedia (online encyclopedia), provide the following simplified definitions of BSA, Lysozyme, Ovalbumin, Myoglobin, Ubiquitin, and Bacteriorhodopsin:

- BSA, is a serum albumin protein. Serum albumin, often referred to simply as albumin, is the most abundant plasma protein in humans and other mammals

- Lysozyme is a 14.4 kilodalton enzyme that damages bacterial cell walls by catalyzing hydrolysis of 1,4-beta-linkages between N-acetylmuramic acid and N-acetyl-D-glucosamine residues in a peptidoglycan and between N-acetyl-D-glucosamine residues in chitodextrins. It is abundant in a number of secretions, such as tears, saliva, and mucus.

- Ovalbumin is the main protein found in egg white, making up 60-65% of the total protein. It belongs to the serpin superfamily of proteins, although unlike the majority of serpins it is unable to inhibit any proteases.

- Myoglobin is a single-chain globular protein of 153 amino acids, containing a heme (iron-containing porphyrin) prosthetic group in the center around which the remaining apoprotein folds. It has a molecular weight of 16,700 daltons, and is the primary oxygen-carrying pigment of muscle tissues

- Ubiquitin is a highly-conserved small regulatory protein that is ubiquitous in eukaryotes

- Bacteriorhodopsin is an integral membrane protein usually found in two-dimensional crystalline patches known as "purple membrane", which can occupy up to nearly 50% of the surface area of the archaeal cell. ... Each chain has seven transmembrane

alpha helices and contains one molecule of retinal buried deep within, the typical structure for retinylidene proteins.

The number of proteins/peptides disclosed in the instant specification are of varying size and utility, as well as cellular location as to satisfy the requirement of a representative number of species.

****

Much of the Wands factors analysis appears to be directed to the claims as pending in the prior office action, for example, Factors 1), 7) and 8) specifically mention the language "enhancing any chemical reaction" or "any chemical reaction." The Examiner is respectfully reminded that such language was removed from the claim in favor of the language "enhancing chemical digestion, chemical alteration, or a combination thereof." However, for the sake of clarity and completeness, Applicants shall address the remaining Wands factors in turn:

2) The Office Action suggests that the "nature of the invention is directed to methods of solubilizing proteins with a dioxolan surfactant." Applicants disagree and respectfully invite the Examiner's attention to the Initial Remarks of this Response, emphasizing that the instantly claimed invention is directed to chemical digestion and alteration of proteins and peptides, which does not include purely physical changes alone, such as solubilization.

3) The Office Action also suggests that the "relative level of skill possessed by one of ordinary skill in the art of chemical research is relatively high …" Applicants shall abstain from comment at this time with respect to this statement.

4) The Office Action suggests the "art teaches that dioxolans of the instant invention are useful for solubilizing proteins (See claims 27-31 in Lee et al. WO 00/70334)." And "Taramellii et al. teach that malaria pigment β-hematin is an insoluble biomolecule (Abstract)." Applicants again point to our Initial Remarks and highlight that the instantly claimed invention

is not directed to solubilization alone; but rather is directed to chemical digestion and alteration of proteins or peptides, some of which may also produce soluble products.

5) The Office Action again attempts to focus on the issue of solubility, and its unpredictability, by suggesting that "the art teaches that not all proteins may completely dissolve in the presence of surfactants. Applicants point out that not only does this not have bearing on a surfactant that is different from those cited, but is not relevant to the instantly claimed invention directed to chemical digestion and alteration of proteins or peptides.

6) The Office Action suggests that "[a]lthough the instant specification discloses that a method of enhancing the solubility of the proteins BSA, lysozyme, ovalbumin, ubiquitin, and bacteriorhodopsin…with the claimed dioxolan surfactant ALS, it remains silent on enhancing any chemical reaction with any molecule with the surfactant." Applicants respectfully disagree. The instant application discloses numerous examples of chemical digestion and alteration of biomolecules, *e.g.*, proteins and peptides. Example 3, Table 2, and Figure 2 clearly show an increase in digestion of various biomolecules in the presence of a surfactant of formula I. Examples 4 and 5 also demonstrate the digestion of various biomolecules in the presence of a surfactant of formula I. Additionally, Example 8 and Figure 5 shows a chemical alteration of a disulfide bond in the presence of a surfactant. Specifically, Figure 5 demonstrates the reduction of a disulfide bond both in the presence and absence of a surfactant. Applicants therefore contend that the numerous working examples provided in the specification fully enables the scope of the amended claims.

****

With respect to the Examiner's "**Response to Arguments**," the Office Action alleges that "solubilization is encompassed by chemical alteration and the art teaches insoluble biomolecules." Applicant refers the Examiner to the Initial Remarks section and emphasizes that it would be clear to the ordinarily skilled artisan that the term ***chemical*** alteration was not intended to encompass purely *physical* changes alone such as "solubilization." In fact, the ordinarily skilled artisan would understand, that a physical change, such as solubilization, may

occur as a result of a chemical reaction or chemical alteration, but that solubilization on its own, is a ***physical*** change (and not a chemical change). As such, the art which teaches insoluble biomolecules is not applicable to the present invention.

Applicants respectfully submit that the claims presented herein are fully enabled by the application and, therefore, request reconsideration and withdrawal of the enablement rejection.

Claim Rejections – 35 U.S.C. § 102

Claims 1-9, 11, 20-30, and 33 are rejected under 35 U.S.C. §102(b)

Claims 1-9, 11, 20-30, 33 and 123 are rejected under 35 U.S.C. §102(b) as being anticipated by Lee, *et al.* (WO 00/70334). The Office Action, on page 7, again sets forth the allegation that WO 00/70334 discloses a method of solubilizing a substance comprising contacting the substance with a surfactant of Applicants' formula I, and that "solubilizing" reads on "enhancing a chemical reaction." Applicants respectfully disagree and traverse the rejection. The Examiner is respectfully reminded that such language was removed from the claim in favor of the language "enhancing chemical digestion, chemical alteration, or a combination thereof .

Additionally, with respect to the Examiner's "**Response to Arguments**," the Office Action alleges that "solubilization is encompassed by chemical alteration and is anticipated by Lee et al." based on what the Examiner has inferred from the language of the specification. As noted above, Applicants disagree with this statement and respectfully request that the Examiner review Applicants Initial Remarks, which are incorporated herein by reference thereto.

At emphasis therein was ***above all, the chemical alteration***, while possibly producing *altered* molecules that are soluble, ***must involve a chemical reaction at the very least***. Moreover, it was the intention of this definition, and a definition consistent with the understanding of the ordinarily skilled artisan, to provide language that would contrast two types of chemical reactions. One type of chemical reaction involves a strict breaking down reaction of a molecule into fragments, while the other type of chemical reaction simply involves a "chemical transformation or change," as described in the definition of the language "chemical

reaction" on page 8, lines 1- 2 of the instant specification. It would be clear to the ordinarily skilled artisan that the term ***chemical*** alteration was not intended to encompass purely *physical* changes alone such as "solubilization." In fact, the ordinarily skilled artisan would understand, that a physical change, such as solubilization, may occur as a result of a chemical reaction or chemical alteration, but that solubilization on its own, is a ***physical*** change (and not a chemical change). As such, the interpretation set forth in the Office Action is not consistent with the knowledge of the ordinarily skilled artisan, and is therefore improper.

Accordingly, Applicants request withdrawal of the rejection of claims 1-9, 11, 20-30, 33 and 123 under 35 U.S.C. §102(b), and favorable reconsideration

Claim Rejections – 35 U.S.C. § 103

Claims 1-9, 11-30, and 33 are rejected under 35 U.S.C. §103(a)

Claims 1-9, 11-30, 33 and 123 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lee, *et al.* (WO 00/70334) in view of Zee Yong et al. (Anal. Chem. 2001, 73, 2558-2564) and Nelson (US 6,093,541). Applicants respectfully disagree and traverse the rejection.

Moreover, it has been asserted in the Office Action that: (1) Lee teaches a method of solubilizing a substance using a surfactant of the invention and that solubilization reads on the language "chemical alteration"; (2) Zee-Yong et al. teach identification of individual proteins in a complex mixture by MALDI mass spectrometry; and (3) Nelson teaches proteases for use in mass spectrometers.

Applicants have asserted herein above that the teaching of Lee et al. related to solubilization does not anticipate or make the instantly claimed invention obvious. The Examiner has repeated alleged that solubilization is encompassed by chemical alteration and is anticipated by Lee et al. based on what the Examiner has inferred from the language of the specification. As noted above, Applicants disagree with this statement and respectfully request that the Examiner review Applicants Initial Remarks, which are incorporated herein by reference thereto.

At emphasis in these Remarks is that ***above all, that the chemical alteration***, while possibly producing *altered* molecules that are soluble, ***must involve a chemical reaction at the very least***. Moreover, it was the intention of this definition, and a definition consistent with the understanding of the ordinarily skilled artisan, to provide language that would contrast two types of chemical reactions. One type of chemical reaction involves a strict breaking down reaction of a molecule into fragments, while the other type of chemical reaction simply involves a "chemical transformation or change," as described in the definition of the language "chemical reaction" on page 8, lines 1- 2 of the instant specification. It would be clear to the ordinarily skilled artisan that the term ***chemical*** alteration was not intended to encompass purely *physical* changes alone such as "solubilization." In fact, the ordinarily skilled artisan would understand, that a physical change, such as solubilization, may occur as a result of a chemical reaction or chemical alteration, but that solubilization on its own, is a ***physical*** change (and not a chemical change). As such, the interpretation set forth in the Office Action is not consistent with the knowledge of the ordinarily skilled artisan, and is therefore improper.

Accordingly, the difference between the prior art and the pending claims, is the ***entire claimed invention***. In this regard, once it has been established that solubilization does not fall within the scope of the language "chemical alteration," it would be understood that there is **absolutely no overlap between the prior art and the instantly pending claims**. To this end, the prior art does not teach or suggest all of the claim limitations, nor would there be a reasonable expectation of success in achieving the enhanced chemical alteration or chemical digestion of the claimed invention using the references cited, alone or in combination. Therefore, Applicants submit that the Office Action has failed to establish a *prima facie* case of obviousness.

However, assuming *arguendo* that a prima facie case has been made, Applicants assert that, in contrast to the references cited *supra*, ***the instant invention clearly demonstrates the unexpected results and advantages of using a surfactant to enhance a chemical digestion or alteration of a protein or peptide as presently claimed***. Such advantages include more rapid, reproducible, relatively low temperature digestion of a protein or peptide, which requires less protease due to enhanced efficiency of the reaction without concomitant increase in miscleavages. Such reactions result in more complete reactions and afford an increased number of correctly cleaved fragments (page 3, lines 5-12). Additional unexpected results and

advantages of the instant invention include greater mass spectrometric sensitivity in the presence of the surfactants, even in the presence of degradation products (page 5, lines 26-29).

****

Based on the foregoing, Applicants submit that the teachings in WO 00/70334, whether alone or in combination with Zee-Yong et al. and/or Nelson, do not teach or suggest Applicants' claimed subject matter. As such, Applicants request that the rejection be withdrawn and favorable reconsideration.

Obviousness-type Double Patenting

Claims 1-7, 22, 23, and 25-27 are provisionally rejected in view of Application No. 10/169,002. Applicants again request that this provisional rejection be held in abeyance until allowance of the instant claims, but for the obviousness-type double patenting rejection.

CONCLUSION

It is believed the application is in condition for immediate allowance, which action is earnestly solicited. Should any of the claims not be found to be allowable, the Examiner is requested to telephone Applicants' undersigned representative at the number below. Applicants thank the Examiner in advance for this courtesy. The Examiner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Dated: January 29, 2008

Respectfully submitted,

By /Jacob G. Weintraub/
Jacob G. Weintraub, Reg. No.: 56,469
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 239-0100
Attorneys/Agents For Applicant